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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/516,629	12/01/2004	Detlef P Muller-Schulte	RO0940US(#90568)	4567

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EXAMINER	
JUNG, UNSU	
ART UNIT	PAPER NUMBER
1641	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	01/11/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/516,629	MULLER-SCHULTE, DETLEF P	
	Examiner	Art Unit	
	Unsu Jung	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 October 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-44 and 46-67* is/are pending in the application.

4a) Of the above claim(s) *1-24,43,44,46,47 and 63-65* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *25-42,48-62,66 and 67* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/16/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendment

1. Amendments to add new claims 66 and 67 in the reply field on October 10, 2006 have been acknowledged and entered.

2. Claims 1-44 and 46-67 are pending and claims 25-42, 48-62, 66, and 67 are under consideration for their merits.

Information Disclosure Statement

3. The information disclosure statement filed on October 16, 2006 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each cited foreign patent document; each non-patent literature publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. It has been placed in the application file, but the non-patent literature publications listed on pp5-8 have not been considered as no copy of each non-patent literature publication or that portion which caused it to be listed has been provided.

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

6. Claims 25-33, 38, 49-54, and 58 are rejected under 35 U.S.C. 103(a) as being unpatentable over Müller-Schulte (U.S. Patent No. 6,204,033, Mar. 20, 2001) in view of Kondo et al. (*J. Fermentation and Bioengineering*, 1997, Vol. 84, pp337-341).

Müller-Schulte teaches a process for a production of polymers containing at least one of magnetic or metallic colloids, the process comprising steps of dispersing at least one of encapsulated magnetic or metallic colloids in an aqueous monomer solution, suspending the aqueous monomer solution in an organic phase that is not miscible with water after addition of a radical initiator and radically polymerizing the organic phase to nano- or micro-particles (Abstract and column 7, lines 19-55). However, Müller-Schulte fails to teach a process, wherein the monomer solution contains a thermosensitive monomer suspended through mechanical communition and further adding a cross-linking agent to form thermosensitive polymers having a physical structure changeable by magnetic induction.

Kondo et al. teaches a method of polymerizing magnetic particles by co-polymerizing N-isopropylacrylamide (NIPAM), methacrylic acid (MAA) and N,N'-methylene-bis-acrylamide (MBA, Abstract). Crosslinking reagent MBA is used to increase the mechanical strength of the microspheres (p338, left column, first paragraph). The polymerization process involves stirring (mechanical communition) of a suspension of monomers, crosslinking reagent and a radical initiator (potassium persulfate, KPS, pp337-338, *Preparation and characterization of thermo-sensitive magnetic hydrogel microspheres*). The thermo-sensitive nature of NIPAM enables reversible transition of microspheres between dispersion and flocculation as a function of temperature (p337, left column, second paragraph). The thermoflocculated microspheres can be separated quickly from solutions in a relatively low magnetic field and can be used for carriers for affinity purification (p337, left column, second paragraph).

Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention to include the method of polymerizing encapsulated magnetic particles of Müller-Schulte by suspension of N-isopropylacrylamide (NIPAM), methacrylic acid (MAA) and N,N'-methylene-bis-acrylamide (MBA) through mechanical communition after adding a crosslinking reagent (MBA) and a radical initiator as taught by Kondo et al. in order to generate thermosensitive polymeric particles having a physical structure changeable by magnetic induction. The advantages of the thermo-sensitive nature of NIPAM, which enables reversible transition of microparticles between dispersion and flocculation as a function of temperature (induced by a low

magnetic field) and use of a crosslinking agent, which increases the mechanical strength of the microparticles, provide the motivation to combine the methods of Kondo et al. with the methods of Müller-Schulte as the thermosensitive particles can be separated quickly from solution in a relatively low magnetic field, which would be advantageous in an affinity purification assays. In addition, one of ordinary skill in the art at the time of the invention would have had a reasonable expectation of success since Müller-Schulte demonstrates that the encapsulated microparticles can be further polymerized.

With respect to claims 28, 29, 49, and 50, Kondo et al. teaches a process, further comprising the step of adding co-monomers to the monomer solution to obtain resulting copolymers, wherein the co-monomers are acrylic acid (MAA), having a co-monomer content of the resulting copolymers being between 0.05 and 30% by mol. (p339, Table 1).

With respect to claims 30, 31, 51, and 52, Müller-Schulte teaches a process, further comprising a step of adding a magnetic particle size of 10-200 nm in magnetic colloid form (column 5, lines 38-42).

With respect to claims 32, 33, 53, and 54, Müller-Schulte teaches a process, further comprising steps of dispersively encapsulating the magnetic or metallic colloids in a nano- or micro-particle core polymer and adding the encapsulation to the monomer solution, wherein the core polymer comprises polyvinyl alcohol (Abstract).

With respect to claims 38 and 58, Müller-Schulte teaches a process, further comprising a step of bonding a compound from a group consisting of antibodies,

peptides, proteins, enzymes, streptavidin, oligonucleotides, oligosaccharides, and DNA (Abstract).

7. Claims 34 and 55 are rejected under 35 U.S.C. 103(a) as being unpatentable over Müller-Schulte (U.S. Patent No. 6,204,033, Mar. 20, 2001) in view of Kondo et al. (*J. Fermentation and Bioengineering*, 1997, Vol. 84, pp337-341), as applied to claim 25 above, and further in view of Shishikura et al. (U.S. Patent No. 5,990,262, Nov. 23, 1999).

Müller-Schulte in view of Kondo et al. teaches a process for a production of thermosensitive polymers as discussed above. Müller-Schulte further teaches that organic solvents such as hexane, heptane, cyclohexane, or petroleum ether are used in the process for the production of the thermosensitive polymers (column 7, lines 45-51). However, Müller-Schulte fails to specifically disclose that these organic phase solvents have a polar solubility parameter of 5-10 $(cal/cm^3)^{1/2}$.

Shishikura et al. teaches that heptane has a solubility parameter of 7.4 $(cal/cm^3)^{1/2}$. Therefore, one of ordinary skill in the art would recognize that the organic solvent of Müller-Schulte would inherently have solubility parameter of 7.4 $(cal/cm^3)^{1/2}$.

8. Claims 35, 36, 56, and 57 are rejected under 35 U.S.C. 103(a) as being unpatentable over Müller-Schulte (U.S. Patent No. 6,204,033, Mar. 20, 2001) in view of Kondo et al. (*J. Fermentation and Bioengineering*, 1997, Vol. 84, pp337-341) as applied

to claims 25 and 26 above, and further in view of Klaveness et al. (U.S. Patent No. 4,647,536, Mar. 3, 1987).

Müller-Schulte in view of Kondo et al. teaches a process for a production of thermosensitive polymers as discussed above. However, Müller-Schulte in view of Kondo et al. fails to teach a process, further comprising the step of adding at least one surfactive substances to the organic phase at 0.05 to 0.15% by weight, wherein the surfactive substance is polyoxyethylenes.

Klaveness et al. teaches a method of using surfactants such as polyoxyethylenes typically in amounts of 1-10% w/v to stabilize the resulting oil in water emulsion during emulsification process for making polymeric particles (column 11, lines 21-56).

Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention to include polyoxyethylenes as a surfactant in 1-10% w/v in the suspension of magnetic colloids and monomers of Müller-Schulte in view of Kondo et al. with as taught by Klaveness et al. in order to stabilize the suspension of aqueous monomer solution in non-miscible organic phase during emulsification process (stirring). The advantage of forming a stabilized suspension of aqueous monomer solution in non-miscible organic phase during emulsification process provides the motivation for including the polyoxyethylenes of Klaveness et al. as a surfactant in the method of Müller-Schulte in view of Kondo et al. In addition, one of ordinary skill in the art at the time of the invention would have had a reasonable expectation of success since an addition of a surfactant such as polyoxyethylenes would stabilize the suspension of

aqueous monomer solution in non-miscible organic phase in a method for forming polymeric particles.

9. Claim 37 is rejected under 35 U.S.C. 103(a) as being unpatentable over Müller-Schulte (U.S. Patent No. 6,204,033, Mar. 20, 2001) in view of Kondo et al. (*J. Fermentation and Bioengineering*, 1997, Vol. 84, pp337-341) as applied to claim 25 above, and further in view of Minghetti et al. (U.S. Patent No. 5,415,931, May 16, 1995).

Müller-Schulte in view of Kondo et al. teaches a process for a production of thermosensitive polymers as discussed above. However, Müller-Schulte in view of Kondo et al. fails to teach a process for a production of thermosensitive polymers, further comprising a step of pre-polymerizing the monomer solution for 5-120 seconds before dispersion in the organic phase.

Minghetti et al. teaches a method of pre-polymerizing a portion of monomers before final polymerization process in order to more readily control the polymerization process and the size and shape of the polymer (column 1, lines 27-33).

Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention to include in the method of Müller-Schulte in view of Kondo et al. an additional step of pre-polymerizing the monomer solution before dispersion in the organic phase for final polymerization as taught by Minghetti et al. in order to more readily control the polymerization process and the size and shape of the polymeric particles. The advantage of controlling the polymerization process and the size and shape of the polymeric particles provides the motivation for combining the methods of

Minghetti et al. and Müller-Schulte in view of Kondo et al. In addition, one of ordinary skill in the art at the time of the invention would have had a reasonable expectation of success in combining the methods of Minghetti et al. and Müller-Schulte in view of Kondo et al. since the pre-polymerization methods have been shown to control the polymerization process and the size and shape of the polymers. With respect to the limitation of "pre-polymerizing the monomer solution for 5-120 seconds", Müller-Schulte in view of Kondo et al. and Minghetti et al. discloses the claimed invention except for pre-polymerizing the monomer solution for 5-120 seconds. It would have been obvious to one of ordinary skill in the art at the time of the invention to pre-polymerize the monomer solution for 5-120 seconds, since it has been held that where the general conditions of a claim are disclosed in the prior art, discovering the optimum or workable ranges involves only routine skill in the art. *In re Aller*, 105 USPQ 233.

10. Claims 39, 40, 59, and 60 are rejected under 35 U.S.C. 103(a) as being unpatentable over Müller-Schulte (U.S. Patent No. 6,204,033, Mar. 20, 2001) in view of Kondo et al. (*J. Fermentation and Bioengineering*, 1997, Vol. 84, pp337-341) as applied to claims 25 and 26 above, and further in view of Mosbach et al. (U.S. Patent No. 4,647,536, Mar. 3, 1987).

Müller-Schulte in view of Kondo et al. teaches a process for a production of thermosensitive polymers as discussed above. However, Müller-Schulte in view of Kondo et al. fails to teach a process for a production of thermosensitive polymers, further comprising a step of encapsulating active agents in the polymers by adding the

active agents to a monomer solution containing at least one of magnetic or metallic colloids.

Mosbach et al. teaches a method of encapsulating enzymes by bead polymerization process, where the monomer solution together with enzyme is dispersed in hydrophobic phase (column 1, lines 31-34).

Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention to include a step of adding encapsulating active agents (enzymes) in the polymers by adding the active agents to a monomer solution containing at least one of magnetic or metallic colloids of Müller-Schulte in view of Kondo et al. as taught by Mosbach et al. in order to encapsulate active agents by microparticle polymerization process. The advantage of performing both the encapsulation and polymerization processes in one step provides the motivation of combining the methods of Mosbach et al. and Müller-Schulte in view of Kondo et al. In addition, one of ordinary skill in the art at the time of the invention would have had a reasonable expectation of success since Mosbach et al. demonstrated that encapsulating active agents such as enzymes (proteins) can be performed during the polymerization step.

11. Claims 41, 42, 61, and 62 are rejected under 35 U.S.C. 103(a) as being unpatentable over Müller-Schulte (U.S. Patent No. 6,204,033, Mar. 20, 2001) in view of Kondo et al. (*J. Fermentation and Bioengineering*, 1997, Vol. 84, pp337-341) and of Mosbach et al. (U.S. Patent No. 4,647,536, Mar. 3, 1987) as applied to claims 40 and 60 above, and further in view of Khan et al. (U.S. Patent No. 5,413,797, May 9, 1995).

Müller-Schulte in view of Kondo et al. teaches a process for a production of thermosensitive polymers as discussed above. However, Müller-Schulte in view of Kondo et al. fails to teach a process for a production of thermosensitive polymers, further comprising a step of adding a compound selected from the consisting of polyvalent alcohols, polyvinyl alcohols, gelatins and carbohydrates are added to the active agents in an amount of 0.1 to 20% by weight, wherein the polyvalent alcohols or carbohydrates are selected from the group consisting of inosite, mannite, sorbite, aldonite, erythrite, sucrose, glycerine, xylite, fructose, glucose, galactose and maltose.

Khan et al. teaches a method of adding a stabilizer for to an active agent (ACTH, column 7, lines 26-37). The examples of stabilizers include carbohydrates such as sucrose (column 7, lines 24-33). The amount of carbohydrates to protein generally ranges from 1:10 to 4:1 (column 7, lines 34-36).

Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention to add a stabilizer to the active agent as taught by Khan et al. in the method of Müller-Schulte in view of Kondo et al. and Mosbach et al. in order to enhance stability of the active agent. The advantage of stabilizing the active agent in the thermosensitive polymers provides the motivation of combining the methods of Khan et al. and Müller-Schulte in view of Kondo et al. and Mosbach et al. In addition, one of ordinary skill in the art at the time of the invention would have had a reasonable expectation of success in combining the methods of Khan et al. and Müller-Schulte in view of Kondo et al. and Mosbach et al. since the stabilizer of Khan et al. stabilizes a

protein molecules, which are the active agents of the thermosensitive polymers of Müller-Schulte in view of Kondo et al. and Mosbach et al.

New Grounds of Rejection

12. Claims 66 and 67 are rejected under 35 U.S.C. 103(a) as being unpatentable over Müller-Schulte (U.S. Patent No. 6,204,033, Mar. 20, 2001) in view of Kondo et al. (*J. Fermentation and Bioengineering*, 1997, Vol. 84, pp337-341) and Murayama et al. (U.S. Patent No. 5,672,656, Sept. 30, 1997).

Müller-Schulte teaches a process for a production of polymers containing at least one of magnetic or metallic colloids as discussed above. However, Müller-Schulte fails to teach a process, wherein the monomer solution contains a thermosensitive monomer suspended through mechanical communition and further adding a cross-linking agent to form thermosensitive polymers having a physical structure changeable by magnetic induction, wherein the radical initiator is a N,N,N',N'-tetramethylene diamine and ammonium persulphate.

Kondo et al. teaches a method of polymerizing magnetic particles by co-polymerizing N-isopropylacrylamide (NIPAM), methacrylic acid (MAA) and N,N'-methylene-bis-acrylamide (MBA) as discussed above.

Murayama et al. teaches a method of using N,N,N',N'-tetramethylene diamine and ammoninum persulphate as a radical initiator, which is a suitable water-soluble radical initiator (column 4, lines 11-27).

Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention to include the method of polymerizing encapsulated magnetic particles of Müller-Schulte by suspension of N-isopropylacrylamide (NIPAM), methacrylic acid (MAA) and N,N'-methylene-bis-acrylamide (MBA) through mechanical communition after adding a crosslinking reagent (MBA) and a radical initiator as taught by Kondo et al. in order to generate thermosensitive polymeric particles having a physical structure changeable by magnetic induction. The advantages of the thermo-sensitive nature of NIPAM, which enables reversible transition of microparticles between dispersion and flocculation as a function of temperature (induced by a low magnetic field) and use of a crosslinking agent, which increases the mechanical strength of the microparticles, provide the motivation to combine the methods of Kondo et al. with the methods of Müller-Schulte as the thermosensitive particles can be separated quickly from solution in a relatively low magnetic field, which would be advantageous in an affinity purification assays. In addition, one of ordinary skill in the art at the time of the invention would have had a reasonable expectation of success since Müller-Schulte demonstrates that the encapsulated microparticles can be further polymerized. Further, Müller-Schulte in view of Kondo et al. discloses the claimed invention except for the use of N,N,N',N'-tetramethylene diamine and ammoninum persulphate as the radical initiator. It would have been obvious to one of ordinary skill in the art at the time of the invention to employ a generally well known system of radical initiator such as using N,N,N',N'-tetramethylene diamine and ammoninum persulphate of Murayama et al., since it has been held that discovering optimum value of a result

effective variable involves only routine skill in the art. In re Boesch, 617 F. 2d 272, 205 USPQ 215 (CCPA 1980).

Double Patenting

13. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

14. Claims 25-33, 38, 49-54, and 58 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-9 and 14 of U.S. Patent No. 6,204,033 in view of Kondo et al. (*J. Fermentation and Bioengineering*, 1997, Vol. 84, pp337-341).

U.S. Patent No. 6,204,033 teaches a process for a production of polymers containing at least one of magnetic or metallic colloids, the process comprising steps of dispersing at least one of encapsulated magnetic or metallic colloids in an aqueous monomer solution, suspending the aqueous monomer solution in an organic phase that is not miscible with water after addition of a radical initiator and radically polymerizing

the organic phase to nano- or micro-particles. However, U.S. Patent No. 6,204,033 fails to teach a process, wherein the monomer solution contains a thermosensitive monomer suspended through mechanical communition and further adding a cross-linking agent to form thermosensitive polymers having a physical structure changeable by magnetic induction.

Kondo et al. teaches a method of polymerizing magnetic particles by co-polymerizing N-isopropylacrylamide (NIPAM), methacrylic acid (MAA) and N,N'-methylene-bis-acrylamide (MBA, Abstract). Crosslinking reagent MBA is used to increase the mechanical strength of the microspheres (p338, left column, first paragraph). The polymerization process involves stirring (mechanical communition) of a suspension of monomers, crosslinking reagent and a radical initiator (potassium persulfate, KPS, pp337-338, *Preparation and characterization of thermo-sensitive magnetic hydrogel microspheres*). The thermo-sensitive nature of NIPAM enables reversible transition of microspheres between dispersion and flocculation as a function of temperature (p337, left column, second paragraph). The thermoflocculated microspheres can be separated quickly from solutions in a relatively low magnetic field and can be used for carriers for affinity purification (p337, left column, second paragraph).

Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention to include the method of polymerizing magnetic particles of U.S. Patent No. 6,204,033 by suspension of N-isopropylacrylamide (NIPAM), methacrylic acid (MAA) and N,N'-methylene-bis-acrylamide (MBA) through mechanical communition

after adding a crosslinking reagent (MBA) and a radical initiator as taught by Kondo et al. in order to generate thermosensitive polymeric particles having a physical structure changeable by magnetic induction. The advantages of the thermo-sensitive nature of NIPAM, which enables reversible transition of microparticles between dispersion and flocculation as a function of temperature (induced by a low magnetic field) and use of a crosslinking agent, which increases the mechanical strength of the microparticles, provide the motivation to combine the methods of Kondo et al. with the methods of U.S. Patent No. 6,204,033 as the thermosensitive particles can be separate quickly from solution in a relatively low magnetic field, which would be advantageous in an affinity purification assays. In addition, one of ordinary skill in the art at the time of the invention would have had a reasonable expectation of success since U.S. Patent No. 6,204,033 demonstrates that the encapsulated microparticles can be further polymerized.

15. Claims 34 and 55 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-9 and 14 of U.S. Patent No. 6,204,033 in view of Kondo et al. (*J. Fermentation and Bioengineering*, 1997, Vol. 84, pp337-341), as applied to claim 25 above, and further in view of Shishikura et al. (U.S. Patent No. 5,990,262, Nov. 23, 1999).

U.S. Patent No. 6,204,033 in view of Kondo et al. teaches a process for a production of thermosensitive polymers as discussed above. U.S. Patent No. 6,204,033 further teaches that organic solvents such as hexane, heptane, cyclohexane, or

petroleum ether are used in the process for the production of the thermosensitive polymers. However, U.S. Patent No. 6,204,033 fails to specifically disclose that these organic phase solvents have a polar solubility parameter of 5-10 $(cal/cm^3)^{1/2}$.

Shishikura et al. teaches that heptane has a solubility parameter of 7.4 $(cal/cm^3)^{1/2}$. Therefore, one of ordinary skill in the art would recognize that the organic solvent of U.S. Patent No. 6,204,033 would inherently have solubility parameter of 7.4 $(cal/cm^3)^{1/2}$.

16. Claims 35, 36, 56, and 57 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-9 and 14 of U.S. Patent No. 6,204,033 in view of Kondo et al. (*J. Fermentation and Bioengineering*, 1997, Vol. 84, pp337-341) as applied to claims 25 and 26 above, and further in view of Klaveness et al. (U.S. Patent No. 4,647,536, Mar. 3, 1987).

U.S. Patent No. 6,204,033 in view of Kondo et al. teaches a process for a production of thermosensitive polymers as discussed above. However, U.S. Patent No. 6,204,033 in view of Kondo et al. fails to teach a process, further comprising the step of adding at least one surfactive substances to the organic phase at 0.05 to 0.15% by weight, wherein the surfactive substance is polyoxyethylenes.

Klaveness et al. teaches a method of using surfactants such as polyoxyethylenes typically in amounts of 1-10% w/v to stabilize the resulting oil in water emulsion during emulsification process for making polymeric particles (column 11, lines 21-56).

Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention to include polyoxyethylenes as a surfactant in 1-10% w/v in the suspension of magnetic colloids and monomers of U.S. Patent No. 6,204,033 in view of Kondo et al. with as taught by Klaveness et al. in order to stabilize the suspension of aqueous monomer solution in non-miscible organic phase during emulsification process (stirring). The advantage of forming a stabilized suspension of aqueous monomer solution in non-miscible organic phase during emulsification process provides the motivation for including the polyoxyethylenes of Klaveness et al. as a surfactant in the method of U.S. Patent No. 6,204,033 in view of Kondo et al. In addition, one of ordinary skill in the art at the time of the invention would have had a reasonable expectation of success since an addition of a surfactant such as polyoxyethylenes would stabilize the suspension of aqueous monomer solution in non-miscible organic phase in a method for forming polymeric particles.

17. Claim 37 is rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-9 and 14 of U.S. Patent No. 6,204,033 in view of Kondo et al. (*J. Fermentation and Bioengineering*, 1997, Vol. 84, pp337-341) as applied to claim 25 above, and further in view of Minghetti et al. (U.S. Patent No. 5,415,931, May 16, 1995).

U.S. Patent No. 6,204,033 in view of Kondo et al. teaches a process for a production of thermosensitive polymers as discussed above. However, U.S. Patent No. 6,204,033 in view of Kondo et al. fails to teach a process for a production of

thermosensitive polymers, further comprising a step of pre-polymerizing the monomer solution for 5-120 seconds before dispersion in the organic phase.

Minghetti et al. teaches a method of pre-polymerizing a portion of monomers before final polymerization process in order to more readily control the polymerization process and the size and shape of the polymer (column 1, lines 27-33).

Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention to include in the method of U.S. Patent No. 6,204,033 in view of Kondo et al. an additional step of pre-polymerizing the monomer solution before dispersion in the organic phase for final polymerization as taught by Minghetti et al. in order to more readily control the polymerization process and the size and shape of the polymeric particles. The advantage of controlling the polymerization process and the size and shape of the polymeric particles provides the motivation for combining the methods of Minghetti et al. and U.S. Patent No. 6,204,033 in view of Kondo et al. In addition, one of ordinary skill in the art at the time of the invention would have had a reasonable expectation of success in combining the methods of Minghetti et al. and U.S. Patent No. 6,204,033 in view of Kondo et al. since the pre-polymerization methods have been shown to control the polymerization process and the size and shape of the polymers. With respect to the limitation of "pre-polymerizing the monomer solution for 5-120 seconds", U.S. Patent No. 6,204,033 in view of Kondo et al. and Minghetti et al. discloses the claimed invention except for pre-polymerizing the monomer solution for 5-120 seconds. It would have been obvious to one of ordinary skill in the art at the time of the invention to pre-polymerize the monomer solution for 5-120 seconds, since it has

been held that where the general conditions of a claim are disclosed in the prior art, discovering the optimum or workable ranges involves only routine skill in the art. *In re Aller*, 105 USPQ 233.

18. Claims 39, 40, 59, and 60 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-9 and 14 of U.S. Patent No. 6,204,033 in view of Kondo et al. (*J. Fermentation and Bioengineering*, 1997, Vol. 84, pp337-341) as applied to claims 25 and 26 above, and further in view of Mosbach et al. (U.S. Patent No. 4,647,536, Mar. 3, 1987).

U.S. Patent No. 6,204,033 in view of Kondo et al. teaches a process for a production of thermosensitive polymers as discussed above. However, U.S. Patent No. 6,204,033 in view of Kondo et al. fails to teach a process for a production of thermosensitive polymers, further comprising a step of encapsulating active agents in the polymers by adding the active agents to a monomer solution containing at least one of magnetic or metallic colloids.

Mosbach et al. teaches a method of encapsulating enzymes by bead polymerization process, where the monomer solution together with enzyme is dispersed in hydrophobic phase (column 1, lines 31-34).

Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention to include a step of adding encapsulating active agents (enzymes) in the polymers by adding the active agents to a monomer solution containing at least one of magnetic or metallic colloids of U.S. Patent No. 6,204,033 in view of Kondo et al.

as taught by Mosbach et al. in order to encapsulate active agents by microparticle polymerization process. The advantage of performing both the encapsulation and polymerization processes in one step provides the motivation of combining the methods of Mosbach et al. and U.S. Patent No. 6,204,033 in view of Kondo et al. In addition, one of ordinary skill in the art at the time of the invention would have had a reasonable expectation of success since Mosbach et al. demonstrated that encapsulating active agents such as enzymes (proteins) can be performed during the polymerization step.

19. Claims 41, 42, 61, and 62 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-9 and 14 of U.S. Patent No. 6,204,033 in view of Kondo et al. (*J. Fermentation and Bioengineering*, 1997, Vol. 84, pp337-341) and of Mosbach et al. (U.S. Patent No. 4,647,536, Mar. 3, 1987) as applied to claims 40 and 60 above, and further in view of Khan et al. (U.S. Patent No. 5,413,797, May 9, 1995).

U.S. Patent No. 6,204,033 in view of Kondo et al. teaches a process for a production of thermosensitive polymers as discussed above. However, U.S. Patent No. 6,204,033 in view of Kondo et al. fails to teach a process for a production of thermosensitive polymers, further comprising a step of adding a compound selected from the consisting of polyvalent alcohols, polyvinyl alcohols, gelatins and carbohydrates are added to the active agents in an amount of 0.1 to 20% by weight, wherein the polyvalent alcohols or carbohydrates are selected from the group consisting

of inosite, mannite, sorbite, aldonite, erythrite, sucrose, glycerine, xylite, fructose, glucose, galactose and maltose.

Khan et al. teaches a method of adding a stabilizer for to an active agent (ACTH, column 7, lines 26-37). The examples of stabilizers include carbohydrates such as sucrose (column 7, lines 24-33). The amount of carbohydrates to protein generally ranges from 1:10 to 4:1 (column 7, lines 34-36).

Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention to add a stabilizer to the active agent as taught by Khan et al. in the method of U.S. Patent No. 6,204,033 in view of Kondo et al. and Mosbach et al. in order to enhance stability of the active agent. The advantage of stabilizing the active agent in the thermosensitive polymers provides the motivation of combining the methods of Khan et al. and U.S. Patent No. 6,204,033 in view of Kondo et al. and Mosbach et al. In addition, one of ordinary skill in the art at the time of the invention would have had a reasonable expectation of success in combining the methods of Khan et al. and U.S. Patent No. 6,204,033 in view of Kondo et al. and Mosbach et al. since the stabilizer of Khan et al. stabilizes a protein molecules, which are the active agents of the thermosensitive polymers of U.S. Patent No. 6,204,033 in view of Kondo et al. and Mosbach et al.

New Grounds of Rejection

20. Claims 66 and 67 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-9 and 14 of U.S. Patent No.

6,204,033 in view of Kondo et al. (*J. Fermentation and Bioengineering*, 1997, Vol. 84, pp337-341) and Murayama et al. (U.S. Patent No. 5,672,656, Sept. 30, 1997).

U.S. Patent No. 6,204,033 teaches a process for a production of polymers containing at least one of magnetic or metallic colloids. However, U.S. Patent No. 6,204,033 fails to teach a process, wherein the monomer solution contains a thermosensitive monomer suspended through mechanical communition and further adding a cross-linking agent to form thermosensitive polymers having a physical structure changeable by magnetic induction, wherein the radical initiator is a N,N,N',N'-tetramethylene diamine and ammoninum persulphate.

Kondo et al. teaches a method of polymerizing magnetic particles by co-polymerizing N-isopropylacrylamide (NIPAM), methacrylic acid (MAA) and N,N'-methylene-bis-acrylamide (MBA) as discussed above.

Murayama et al. teaches a method of using N,N,N',N'-tetramethylene diamine and ammoninum persulphate as a radical initiator, which is a suitable water-soluble radical initiator as discussed above.

Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention to include the method of polymerizing encapsulated magnetic particles of U.S. Patent No. 6,204,033 by suspension of N-isopropylacrylamide (NIPAM), methacrylic acid (MAA) and N,N'-methylene-bis-acrylamide (MBA) through mechanical communition after adding a crosslinking reagent (MBA) and a radical initiator as taught by Kondo et al. in order to generate thermosensitive polymeric particles having a physical structure changeable by magnetic induction. The

advantages of the thermo-sensitive nature of NIPAM, which enables reversible transition of microparticles between dispersion and flocculation as a function of temperature (induced by a low magnetic field) and use of a crosslinking agent, which increases the mechanical strength of the microparticles, provide the motivation to combine the methods of Kondo et al. with the methods of U.S. Patent No. 6,204,033 as the thermosensitive particles can be separated quickly from solution in a relatively low magnetic field, which would be advantageous in an affinity purification assays. In addition, one of ordinary skill in the art at the time of the invention would have had a reasonable expectation of success since U.S. Patent No. 6,204,033 demonstrates that the encapsulated microparticles can be further polymerized. Further, U.S. Patent No. 6,204,033 in view of Kondo et al. discloses the claimed invention except for the use of N,N,N',N'-tetramethylene diamine and ammoninum persulphate as the radical initiator. It would have been obvious to one of ordinary skill in the art at the time of the invention to employ a generally well known system of radical initiator such as using N,N,N',N'-tetramethylene diamine and ammoninum persulphate of Murayama et al., since it has been held that discovering optimum value of a result effective variable involves only routine skill in the art. In re Boesch, 617 F. 2d 272, 205 USPQ 215 (CCPA 1980).

Response to Arguments

21. Rejection of claims 25-33, 38, 49-54, and 58 under 35 U.S.C. 103(a) as being unpatentable over Müller-Schulte in view of Kondo et al.

Examiner acknowledges and thanks the Applicant for pointing out a typo in the previous Office Action dated June 13, 2006 as the claims 25-33, 38, 49-54, and 58

should be rejected under 35 U.S.C. 103(a) not 102(b) in item 16 on p6 of the Office Action.

Applicant's arguments filed on October 10, 2006 have been fully considered but they are not persuasive in view of previously stated grounds of rejection.

In response to applicant's arguments (pp18-20) against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Applicant's argument that Müller-Schulte fails to teach or disclose "thermosensitive polymers" is not found persuasive, as the combined teachings of Müller-Schulte in view of Kondo et al. teaches "thermosensitive polymers" as discussed in the previous Office Action dated June 13, 2006.

In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., Kondo et al. fails to teach that the active compounds are only accumulated rather than encapsulated is not found persuasive as Müller-Schulte teaches encapsulated active compounds) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). The feature of encapsulating active compounds is subsequently rejected under U.S.C. 103(a) as being unpatentable over Müller-Schulte in view of Kondo et al., and further in view of Mosbach et al.

22. Rejection of claims 34 and 55 under 35 U.S.C. 103(a) as being unpatentable over Müller-Schulte in view of Kondo et al., and further in view of Shishikura et al.

Examiner acknowledges and thanks the Applicant for pointing out a typo in the previous Office Action dated June 13, 2006 as the claims 35, 36, 56, and 57 should be rejected under 35 U.S.C. 103(a) not 102(b) in item 17 on p8 of the Office Action.

Applicant's arguments filed on October 10, 2006 have been fully considered but they are not persuasive in view of previously stated grounds of rejection and response to arguments set forth above.

23. Rejection of claims 35, 36, 56, and 57 under 35 U.S.C. 103(a) as being unpatentable over Müller-Schulte in view of Kondo et al., and further in view of Klaveness et al.

Applicant's arguments filed on October 10, 2006 have been fully considered but they are not persuasive in view of previously stated grounds of rejection and response to arguments set forth above.

24. Rejection of claim 37 under 35 U.S.C. 103(a) as being unpatentable over Müller-Schulte in view of Kondo et al., and further in view of Minghetti et al.

Applicant's arguments filed on October 10, 2006 have been fully considered but they are not persuasive in view of previously stated grounds of rejection and response to arguments set forth above.

25. Rejection of claims 39, 40, 59, and 60 are rejected under 35 U.S.C. 103(a) as being unpatentable over Müller-Schulte in view of Kondo et al., and further in view of Mosbach et al.

Applicant's arguments filed on October 10, 2006 have been fully considered but they are not persuasive in view of previously stated grounds of rejection and response to arguments set forth above.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Therefore, Applicant's argument that Mosbach et al. fails to teach thermosensitive polymers and process of Mosbach would only yield bead which are 0.1-1.0 mm are not found persuasive as the combined teachings of Müller-Schulte in view of Kondo et al. disclose the method of using thermosensitive polymers to form micro-particles.

In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., magnetic compounds which are encapsulated which can be heated by induction for releasing active compounds) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

26. Rejection of claims 41, 42, 61, and 62 under 35 U.S.C. 103(a) as being unpatentable over Müller-Schulte in view of Kondo et al., and further in view of Mosbach et al. and Khan et al.

Applicant's arguments filed on October 10, 2006 have been fully considered but they are not persuasive in view of previously stated grounds of rejection and response to arguments set forth above.

Further, Applicant's argument regarding "spray drying" is not found persuasive as Khan et al. teaches the use of a stabilizer for proteins including carbohydrates such as sucrose as discussed in the previous Office Action dated June 13, 2006. Therefore, one of ordinary skill in the art would have found it obvious to use a variety of carbohydrates, which include sucrose with the active compounds of Müller-Schulte in view of Kondo et al. and Mosbach et al. in order to enhance stability of the active compounds.

27. Double Patenting Rejections

Applicant's arguments filed on October 10, 2006 have been fully considered but they are not persuasive in view of previously stated grounds of rejection and response to arguments set forth above.

28. Since the prior art fulfills all the limitations currently recited in the claims, the invention as currently recited would read upon the prior art.

Conclusion

29. No claim is allowed.

30. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

31. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Unsu Jung whose telephone number is 571-272-8506. The examiner can normally be reached on M-F: 9-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le can be reached on 571-272-0823. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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